Remarks

Claim 34 is pending in the subject application. By this Amendment, Applicants have amended claim 34 and added new claims 35 and 36. Support for the amendments and new claims can be found, for example, in the as-filed sequence listing and substitute sequence listing, fields 220-223. Entry and consideration of the amendments and new claims presented herein is respectfully requested. Accordingly, claims 34-36 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Submitted with this Amendment is a supplemental Information Disclosure Statement for the Examiner's consideration. Applicants request that the references in the IDS be made of record in the subject application.

As an initial matter, Applicants gratefully acknowledge the Examiner's withdrawal of all the objections and rejections in the previous Action. Applicants also thank the Examiner for the interview conducted on March 20, 2007 where the rejections of record were discussed. Also discussed during the course of the interview was the data presented in the as-filed specification demonstrating the superior results observed in the animal models of multiple sclerosis.

Claims 13-33 are rejected under 35 U.S.C. § 103(a) as obvious over Proudfoot *et al.* (2001) and Lusso and Polo (WO 99/33989) in view of Czaplewski *et al.* (U.S. Patent No. 5,965,697). The Office Action indicates that Proudfoot *et al.* teach a RANTES polypeptide produced by a mutation of amino acids 44, 45 and 47 and specifically teach a RANTES polypeptide which is "equivalent to the polypeptide of SEQ ID NO: 1". Lusso and Polo were cited, according to the Office Action, for their teaching of a RANTES polypeptide that has at least 90% identity to the wild-type RANTES polypeptide. The Office Action admits that both the Proudfoot *et al.* and the Lusso and Polo publications are silent with respect to the oral administration of RANTES polypeptides to an individual. The Office Action cites to Czaplewski *et al.* for a teaching that RANTES polypeptides can be orally administered for the treatment of viral diseases, such as HIV. The Office Action also argues that Czaplewski *et al.* teach the treatment of multiple sclerosis comprising the administration of RANTES (citing to column 2, lines 10-19). Applicants, again, respectfully traverse this rejection.

Applicants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. Applicants

respectfully assert that the Czaplewski *et al.* reference relates to disaggregated RANTES mutants, which are useful in HIV treatment. In referring to the prior art, this reference mentions that RANTES may be involved in multiple sclerosis; however, it fails to give guidance on any mutants that may be useful for the treatment of this disease. Indeed, Czaplewski *et al.* fail to teach that the mutants disclosed within that patent can be used for the treatment of multiple sclerosis. Rather, the patent teaches that the disaggregated hRANTES polypeptides disclosed therein can be used to treat inflammatory diseases and conditions such as: transplant rejection, atherosclerosis, arthritis, atopic dermatitis, airway inflammatory disorders such as Rous Sarcoma Virus-induced bronchiolitis, delayed type hypersensitivity (DTH) reactions, glomerular nephritis, asthma, endometriosis and cancers (such as, T cell lymphomas, renal cell carcinoma and Wilms' tumors) (see, for example, column 11, line 14). Notably absent from the list of diseases taught in the patent is multiple sclerosis. Thus, it is respectfully submitted that Czaplewski *et al.* would not have taught, suggested, or motivated one skilled in the art to orally administer the claimed RANTES polypeptide to an individual having multiple sclerosis. Thus, as Czaplewski *et al.* fail to teach RANTES mutants according to the subject application or the oral administration of RANTES mutants for the treatment of multiple sclerosis (only discussing multiple sclerosis in the discussion of background art at column 2), Applicants respectfully submit that a *prima facie* case of obviousness has not been established with respect to the claimed invention.

While Applicants respectfully submit that a *prima facie* case of obviousness has not been established by the Patent Office, Applicants further submit that oral administration of the claimed RANTES homolog (SEQ ID NO: 1) resulted in increased bioavailability and effectiveness as compared to wild-type RANTES polypeptides and/or the same RANTES homolog (SEQ ID NO: 1) provided to a test subject via a different route of administration. It is respectfully submitted that such increased bioavailability and effectiveness would not have been expected by one skilled in the art in view of the teachings of the cited references and that the examples and data provided in the as-filed specification provide evidence pertaining to the non-obviousness of the claimed invention.

The specification clearly indicates that the RANTES homolog of SEQ ID NO: 1, having reduced GAG-binding activity and non-conservative substitutions in the 40's dibasic site, exhibits increased bioavailability and better efficacy when administered orally (see, for example, Results,

pages 23-24 of the as-filed specification). As indicated therein, the RANTES homolog of SEQ ID NO: 1 is able to exert an antagonistic activity for a longer period of time when administered orally. The Example also indicates that the RANTES homolog of SEQ ID NO: 1 was able to inhibit cell recruitment in the peritoneal cavity of animals when administered orally and intraperitoneally. However, a time course study indicated that the orally administered RANTES homolog (SEQ ID NO: 1) inhibited the recruitment of peritoneal cells by RANTES for up to 24 hours whereas the same intraperitoneally administered RANTES homolog was able to inhibit the recruitment of cells for a period of less than 8 hours. Thus, the oral administration of the RANTES homolog of SEQ ID NO: 1 has been demonstrated to have unexpectedly better bioavailability and/or ability to inhibit the recruitment of cells as compared to other routes of administration (*e.g.*, intraperitoneal administration) for the same RANTES homolog.

During the course of the interview of March 20, 2007, the examples (presented within the subject application) were discussed. Particularly, the ability of the orally administered chemokine of SEQ ID NO: 1 to reduce intraperitoneal cell chemotaxis induced by wild-type RANTES for a longer period of time, as compared to intraperitoneally administered mutant RANTES, was discussed. Additionally, the ability of orally administered mutant RANTES to better reduce clinical signs in the EAE mouse model of multiple sclerosis as compared to intraperitoneally administered mutant RANTES was also discussed. The Examiners also inquired as to the doses of mutant chemokine chosen for the differing routes of administration.

Submitted herewith is a Declaration under 37 C.F.R. 1.132 of Dr. Amanda Proudfoot, one of the inventors of the claimed subject matter. As discussed in the Declaration, the dosing amount was chosen on the basis of the ability of each dose to reduce intraperitoneal cell recruitment to baseline levels (*i.e.,* provide a similar *in vivo* biological effect). For orally administered mutant chemokine, a dose of 100 μg per mouse reduced cell recruitment to baseline levels. A dose of 10 μg per mouse reduced intraperitoneal cell recruitment by wild-type RANTES to baseline levels when the mutant RANTES was administered intraperitoneally. As also noted in the Declaration, oral administration of the claimed mutant RANTES was also able to reduce intraperitoneal cell recruitment induced by wild-type RANTES for a period of 24 hours (as compared to 2 hours for intraperitoneally administered mutant RANTES (see Figure 2)). Additionally, the Declaration also indicates that it

would be unexpected that orally administered chemokines would be able to induce such responses *in vivo* as one skilled in the art would expect the chemokine to be degraded during its passage through the digestive tract.

The undersigned also wishes to point out that the thesis of Zoë Johnson, attached in the supplemental IDS filed on this same date, indicates that the intraperitoneally administered mutant RANTES has s serum peak of about 500 ng/ml within about 30 minutes after administration (see Figure 27B, page 139) whereas an average serum peak of about 5.86 ng/ml is observed about 4 hours after the oral administration of the mutant RANTES (see page 23, Results, paragraph 1). This is a serum level that is, roughly, one hundred times greater than the orally administered mutant RANTES achieves, yet the orally administered RANTES exhibits better ability to inhibit wild-type RANTES induced cell chemotaxis than does intraperitoneally administered mutant RANTES (dosages adjusted to exhibit a similar biological effect *in vivo*). Applicants respectfully submit that this is an unexpected benefit of the oral administration of the claimed RANTES polypeptides and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 13-33 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 11, 12, 15, 16, and 19 of co-pending Application No. 10/540,234. While Applicants acknowledge that a Terminal Disclaimer can be filed to overcome this rejection, it is submitted that a double patenting rejection of the obviousness-type is analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103, except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (C.C.P.A. 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985). Accordingly, the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection and the factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 U.S.P.Q. 459 (1966) are applied for establishing a background for determining obviousness under 35 U.S.C. 103, including the consideration of any indicia of non-obviousness, when making the obvious-type double patenting analysis.

Applicants note that the final rejection in this matter broadly characterizes the claims of the '234 application as drawn to the treatment of autoimmune and inflammatory disease comprising the administration of RANTES triple 40's mutants. Applicants respectfully submit that the claims of this application are not obvious over those of the '234 application. Principally, the claims of the '234 application are directed to the treatment of liver autoimmune and liver fibrotic inflammatory disorders (see currently pending claims and the as-filed specification of the '234 application, page 6, lines 19-26) whereas the claims of this application are directed to the treatment of multiple sclerosis. As stated by the Supreme Court in *KSR v. Teleflex* (127 S.Ct. 1727, 1740-1741, 82 USPQ2d 1385, 1396 (2007)), "[r]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness", citing to *In re Kahn*, 441 F. 3d 977, 988 (Fed. Cir. 2006). Applicants submit that there is no articulated basis in the rejection of record indicating why one of ordinary skill in the art would have considered the treatment of multiple sclerosis with the claimed polypeptides obvious over the treatment of liver autoimmune and inflammatory disorders. Thus, it is respectfully submitted that a *prima facie* case of obviousness-type double patenting has not been established in the Office Action. It is respectfully submitted that one skilled in the art, considering the claims of each respective application, would not have considered the treatment of multiple sclerosis (a neurological disorder) with the claimed polypeptide obvious over the claims directed to the treatment of liver autoimmune and liver inflammatory diseases. Accordingly, it is respectfully requested that the obviousness-type double patenting rejection of record be withdrawn.

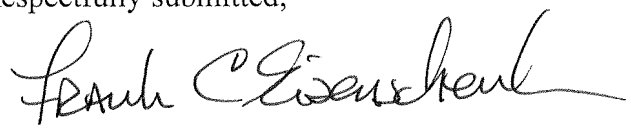
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl

Attachments: Supplemental Information Disclosure Statement
Declaration of Amanda Proudfoot, Ph.D. Under 37 C.F.R. § 1.132